There is nothing in which the birds differ more from man than the way in which they can build yet leave a landscape as it was before.

Robert Straughton Lynd, American sociologist (1892-1970)

Forum

New Mouse Is a Knockout

Scientists have a new tool to help them unravel the mysteries of the toxicity of dioxin. The development of the aryl hydrocarbon receptor-deficient mouse was reported by Frank Gonzalez and colleagues of the National Cancer Institute this May in *Science*.

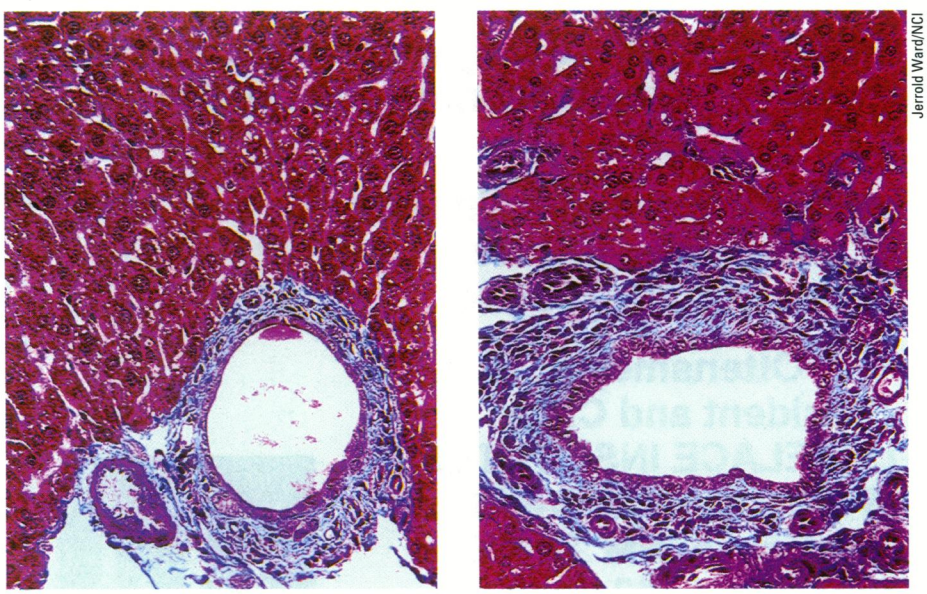
The controversy about the health effects of dioxin partly involves questions about how its toxicity is mediated. Most scientists agree that dioxin exerts its effects by binding to the aryl hydrocarbon receptor (AhR). What is not clear is how this binding relates to the particular cell types that are affected.

The AhR-deficient mouse will help answer questions about the mechanism of dioxin and similar compounds such as benzo[*a*]pyrene, PCBs, and PBBs. Gonzalez and his team produced the mouse by "knocking out" the gene that encodes the AhR. It is known that the AhR detoxifies poisons, but the NCI researchers found evidence that it has other important functions as well.

Half of the AhR-deficient mice die within a week after birth due to a lack of lymphocytes that leaves them susceptible to opportunistic infections. The mice that do survive have massive liver scars and only slowly build up the normal number of lymphocytes. At 10 weeks of age, the animals begin to lose the lymphocytes they built up and eventually become sick due to an incompetent immune system and liver problems. The livers of these mice are 50% smaller than normal, and they have bile duct fibrosis.

The AhR is obviously vital to immune function and liver health. But the depression of the immune system of AhR-deficient mice is a puzzle because the thymus, where T-lymphocytes mature, is normal in these animals. Gonzalez and co-workers hypothesize that AhR-deficient mice may lack a specific lymphoid population or have a systemic defect in the ability of lymphocytes to reside in the peripheral immune system (which includes the reticuloendothelial system, of which the liver is a component). Loss of the AhR may affect thymic processes or affect the migration of cells from the bone marrow (where precursor lymphocytes originate) to the thymus or to peripheral lymphoid organs. Alternatively, the normal life span of peripheral lymphocytes may be shortened in these animals.

Previous research has shown that the AhR may also play a role in brain development. Levels of AhR are high in the fetal neural tube, which gives rise to the central nervous system. Levels decrease after birth. In addition, AhR is found in the kidneys, lungs, and hearts of adults. It is hoped that the AhR-deficient mouse will help clarify the functions of the receptor. However, Gonzalez cautions that experiments with these mice may be difficult because of their poor health. Further genetic engineering may have to be done to turn on the AhR gene only in liver tissue so that the mice will be hardy enough to withstand testing.



Jerrold Ward/NCI

Liver trouble. Accumulation of collagen (blue) around the liver bile duct of a 30-day-old AhR knockout mouse (right) shows the beginning of fibrosis. (Left) Liver bile duct of a normal mouse.

More Muddy Water

In the wake of a report that healthy people can be infected with infinitesimal exposures to *Cryptosporidium* comes the Natural Resources Defense Council's assertion that at least 45 million Americans are at risk of imbibing the diarrhea-causing protozoan in what appears to be clean drinking water.

At the University of Texas in Houston, infectious disease expert Herbert L. DuPont gave 112 healthy volunteers preparations containing between 30 and 1 million *Cryptosporidium* oocysts (the form in which the microbes are found in water). Monitoring enteric symptoms and analyzing stool samples for excreted oocysts, DuPont found that, for the strain he used, the median infective dose was only 132 oocysts. The study suggested the size of the dose did not affect the microbes' incubation period or the severity of the infection.

Just how many people may become infected from their drinking water is impossible to estimate. The NRDC figure of 45 million is based on a survey mailed to 100 of the nation's 61,000 water suppliers, says the organization's president, Eric Olson. The systems who responded serve only a fraction of Americans.

Cryptosporidia give rise to dormant oocysts that remain viable for months in sewage, runoff from feedlots, or groundwater until they find a new host. Unlike other waterborne organisms, the oocysts are neither killed by chlorine nor screened by standard filters, says DuPont. When one member of a household is infected, secondary spread can occur.

Once thought to infect only animals, especially young cattle, *Cryptosporidium* came to the attention of health authorities

in the 1980s, when it was found to cause life-threatening, chronic diarrhea in AIDS patients. In immunocompetent hosts the microbe typically causes a day or two of discomfort, with symptoms including nausea, vomiting, diarrhea, and cramps. Most sufferers need only oral rehydration until they recover.

"Crypto is a nasty nuisance, but not a large-scale public health menace," says DuPont, now at Baylor College of Medicine. Serologic evidence of past infection is found in 15% or more of Americans and nearly 100% of people in tropical areas with poor sanitation. "Here [in the United States] it probably causes many outbreaks of diarrhea in children at day care centers," Dupont said.

But to anyone with impaired immunity, the normally self-limiting illness can be fatal. At risk are patients taking immunosuppressive drugs (to treat cancer or prevent organ transplant rejection), anyone taking steroids, and older people.

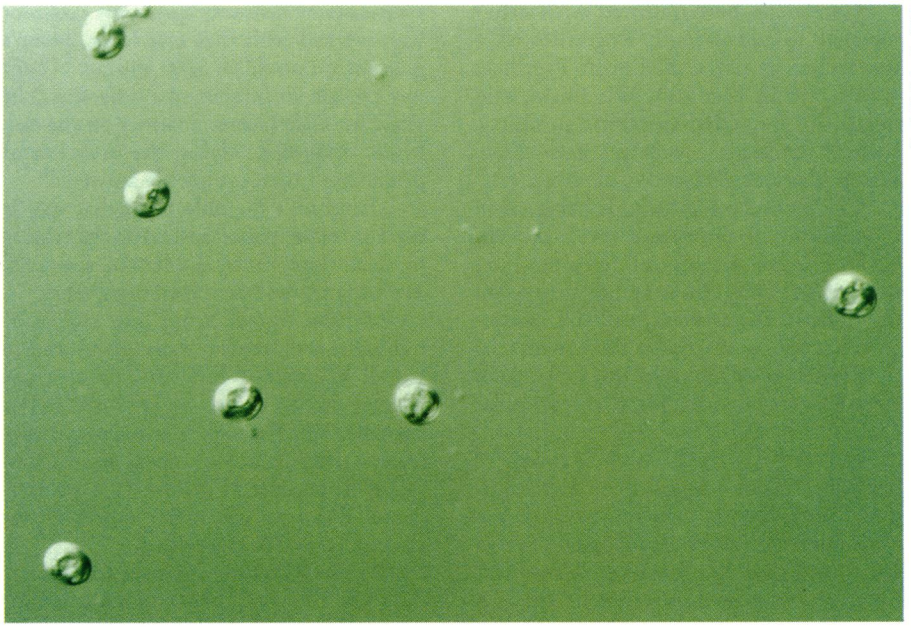
Recent guidelines from the CDC and the EPA say waterborne *Cryptosporidium* can be eliminated by boiling water for one minute or by using a home filtering device to screen particles less than one micron in diameter. Suitable are reverse-osmosis devices, those certified for "cyst removal" by the National Sanitary Foundation, and those labeled as "absolute" for one micrometer.

Point-of-use treatment doesn't satisfy NRDC, however. "Water suppliers shouldn't throw this problem in the lap of those at risk—the sick, the poor, and the elderly. Is it right to ask society's weakest members to boil their drinking water or buy a purifier?" Olson asks.

And expensive bottled water can't be assumed to be oocyte-free unless it's been distilled, properly filtered, or came from a protected spring or other pristine source, something consumers are relatively powerless to determine.

The cost of *Cryptosporidium*-free tap water will vary according to the size of the system, says environmental engineer Stig Regli of the EPA. For an existing major municipal system to add an additional filtering step, or more effective but costlier ozone disinfection would add $10 to $15 per year to a residential water bill, while patrons of small public or private systems might have to pay $100 or more per year, says Regli.

The CDC/EPA guidelines urge individuals who may be worried about *Cryptosporidium* to ask their health care provider about appropriate risk-reducing measures. Current data don't justify telling immunocompromised people to boil or avoid drinking tap water unless there's an outbreak, guidelines say, which warn that narrowly focusing on *Cryptosporidium* (or other single health risk) could draw attention from other potential opportunistic infections.



Frank W. Schaefer/EPA

Drinkable danger. New research shows that relatively small numbers of *Cryptosporidium* oocysts are enough to cause potentially severe infections.

Even the most motivated individual will find absolute safety from *Cryptosporidium* hard to attain. The CDC/EPA guidelines suggest, "Individuals who contact bottlers or filter manufacturers for information should request data supporting claims that a brand of bottled water or filter can meet the above criteria." No agency lists the brands of either safe bottled water or effective home water filter systems, though a list of filters meeting CDC/EPA criteria is available from National Science Foundation (1-800-NSF-8010).

This fall, water systems can enter a voluntary quality control program sponsored by the EPA and the American Waterworks Association, which will certify that they are doing everything feasible to keep the water safe. By participating, systems may shield themselves somewhat from liability if there's a *Cryptosporidium* outbreak similar to the one in 1993 in Milwaukee which incapacitated thousands and led to the deaths of several immunocompromised individuals. "Everybody wants to avoid another Milwaukee," says Regli.

But until and unless water systems eliminate *Cryptosporidium*, DuPont urges anyone with compromised immune function, including anyone over the age of 80, to boil their drinking water, invest in a certified filter, or seek out a reliable brand of bottled water.

Reviving Hemp

Many people know hemp (*Cannabis sativa*), which contains the psychoactive drug tetrahydrocannabinol, as the marijuana plant. But for centuries the Asian herb has been used to make rope or cord, especially large-diameter ropes for ships. Now attention is turning to the use of hemp to make paper.

"It's one of the best fiber sources [for paper] around," says John Ralph, professor of forestry at the University of Wisconsin-Madison. Hemp has long fibers which increase the strength of paper made from it.

Because cultivating marijuana plants is illegal, hemp cannot be grown in the United States. Hemp is widely grown in Hungary and China, and several firms import hemp paper into the United States. Etienne Fontan, a sales manager of the Virginia-based firm Ecolution, touts hemp's environmental advantages. Fontan says that producing hemp paper is more environmentally benign than producing paper from wood. Hemp doesn't require the chlorine bleach and acids used to make paper from wood pulp.

In April of this year, Tree Free EcoPaper of Portland, Oregon, made what it said is the first commercial U.S.-produced hemp-containing paper in 40 years. The paper, made at the company's Massachusetts paper mill, is composed of 10% hemp grown in Europe, plus other nonwoody and recycled materials. According to firm President Paul Stanford, the paper is a high-quality bond paper. Stanford said EcoPaper also plans to use imported hemp to make a lower-grade paper for copiers.